Remarks

Claim 23 and 24 were previously canceled. Claim 1 was amended to specify that the formulation results in diminished incidence or reduced intensity relative to side effects resulting from administration of the same dose of milnacipran in an immediate release formulation. Support for the amendment is found at least at page 8, lines 4-6 and page 13, line 30 to page 14, line 2.

Claim 4 was amended to specify that the peak plasma level was reached at a time between approximately 0.05 hours to less than 3 hours, at a time between approximately 3 hours to less than 14 hours, and at a time between approximately 5 hours to less than 18 hours. Support for the amendment is at least at page 35, line 26 to page 36, line 5.

Claims 5 and 13 was canceled.

Claim 14 was amended to specify that milnacipran is in the form of a therapeutically equivalent dose of para-hydroxy-milnacipran (F2782), individual enantiomers of para-hydroxy-milnacipran, mixtures of enantiomers of para-hydroxy-milnacipran, or pharmaceutically acceptable salts thereof. Support for the amendment is found at least at page 16, lines 23-31.

In the event that this amendment and response does not result in allowance of the claims, the undersigned respectfully requests a personal interview with the Examiner and her supervisor.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 13 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Without making any admissions and solely for the purpose of facilitating prosecution, claim 13 has been canceled.

Rejection Under 35 U.S.C. § 103

Claims 1-10, 15-17, and 19-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,340,476 to Midha *et al.* ("Midha"), in view of Ansseau *et al.*, *Psychopharmacology*, 114, 131-137, (1994) ("Ansseau"). Claims 1-10 and 15-23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Midha in view of Ansseau and Menza *et al.*, *J. Clin. Psychiatry*, 61(5), 378-381 (2000) ("Menza"). Claims 1-13, 15-17, and 19-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Midha in view of Ansseau, further in view of WO 98/08495 to Paillard *et al.* ("Paillard"). Claims 1-3, 6-17, 20, and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2003/0203055 to Rao *et al.* ("Rao"). Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in

KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Supreme Court did not obviate the requirement for the references to provide some motivation to combine as applicants have done, with a reasonable expectation of success. Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> "The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923

(Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Analysis

1. Midha in view of Ansseau

As discussed above, the Court recently reaffirmed the *Graham* factors, which are analyzed below:

(a) Determining the scope and contents of the prior art

Midha

Midha describes pharmaceutical dosage forms for pulsatile release delivery of methylphenidate (available commercially as Ritalin®) ("abstract"). Ritalin® is a central nervous system stimulant that is used for the treatment of Attention Deficit Disorder ("ADD") and Attention Deficit-Hyperactivity Disorder ("ADHD") (col. 2, lines 5-13). Midha is concerned with the pulsatile delivery of methylphenidate due to its potential for tolerance (i.e., loss of clinical efficacy when constant blood levels are maintained) short half-life, and potential for abuse. Milnacipran does not exhibit potential for tolerance or potential for abuse. Midha does not disclose or suggest a milnacipran formulation, or methods of making and using thereof, that provides pulsatile release of milnacipran which exhibits diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects.

Ansseau

Ansseau describes the efficacy and tolerance of fluoxetine versus milnacipran (abstract). Ansseau discloses that fluoxetine showed superior results versus milnacipran (page 135, first paragraph). Ansseau does not disclose or suggest a pulsatile release formulation of milnacipran that exhibits a therapeutic effect over 24 hours or methods of making and using thereof.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The Claimed Compositions

The claimed compositions provide pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. The release profile is characterized in that a first dose is released substantially immediately following oral administration to a patient at a time between approximately 0.5 hours to less than 3 hours following oral administration and a second dose is released as a delayed release dose, resulting in a second plasma peak level at a time between approximately 3 to less than 14 hours following oral administration (claim 4). The formulation may optionally include a

second delayed release dose resulting in a third plasma peak level at a time between approximately 5 hours to less than 18 hours following oral administration (claim 4). The formulation provides milnacipran blood plasma levels that are characterized by a C_{max} below approximately 3000 ng/ml (claim 6), preferably below 2000 ng/ml (claim 7), and more preferably below 1000 ng/ml (claim 8). The formulation can further comprise at least one other active agent (claims 9 and 10).

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. None of the references alone or in combination discloses a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to side effects resulting from administration of the same dose of milnacipran administered in an immediate release formulation, nor is there any teaching leading one of skill in the art to modify to what applicants' claim.

As discussed above, Midha describes pharmaceutical dosage forms for pulsatile release delivery of methylphenidate (available commercially as Ritalin®) ("abstract"). Ritalin® is a central nervous system stimulant that is used for the treatment of Attention Deficit Disorder ("ADD") and Attention Deficit-Hyperactivity Disorder ("ADHD") (col. 2, lines 5-13). Midha is

concerned with the pulsatile delivery of methylphenidate due to its potential for tolerance (i.e., loss of clinical efficacy when constant blood levels are maintained) short half-life, and potential for abuse. Milnacipran does not exhibit potential for tolerance or potential for abuse.

Midha does not disclose or suggest a milnacipran formulation, or methods of making and using thereof, that provides pulsatile release of milnacipran which exhibits diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In fact, Midha does not recognize that pulsatile release formulations can be used to minimize side effects.

Reduction of the incidence and/or severity of side effects of active agents is not an inherent property of pulsatile release formulations. Merely stating that a drug can be administered using a pulsatile release formulation is not sufficient to establish that any given pulsatile release formulation is effective to reduce side effects while still maintaining efficacy. With regard to reducing side effects, although the data presented in Table 1 of the present specification indicates that the incidence of certain adverse events increases with increasing dosage of immediate release milnacipran, it is also clear that increasing dosage does not increase the incidence of certain other side effects. As further shown in Table 1, for several of the side effects that increase with immediate release milnacipran dosage, a linear relationship does not exist between dosage and the incidence of the side effect. For example, the frequency of nausea decreased when increasing dosage from 50 mg/day twice daily to 100 mg/day twice daily, and then increased when increasing dosage from 100 mg/day twice daily to 200 mg/day twice daily.

The effect of dosage amount of milnacipran on the incidence and severity of side effects was not predictable at the time this application was filed view of this data.

Further, Midha does not disclose or suggest that pulsatile release formulations of milnacipran could be developed that produce an efficacious dose over approximately 24 hours. In the formulations described in the present application, the immediate release dosage unit comprises a first dose of an active agent that is released substantially immediately following oral administration of the dosage form to a patient. The delayed release dosage unit comprises a second dose of the active agent and a means for delaying release of the second dose for approximately 3 hours to less than 14 hours following oral administration of the dosage form. The second delayed release dosage unit, when present, comprises a third dose of the active agent and a means for delaying release of the third dose for at least 5 hours to approximately 18 hours following oral administration of the dosage form. These release times indicate that milnacipran will be released from the formulations in disparate gastrointestinal (GI) segments. Drug absorption is known to differ significantly in various GI segments. Physiological factors such as GI transit time, regional pH, surface area, enzymatic activity, manner of transport (i.e. passive vs. active) and microflora all contribute to the variability in absorption (*see*, Rouge, et al., *Int. J. Pharma.*, 136:117-139 (1996), attached). In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine and colon. However, individual drugs can vary widely in their GI absorption spectra. For example, drugs such as vasopressin, benazepril and piretanide all display reduced absorption in the colon

compared to other GI segments, while metroprolol and glibenclamide display similar absorption in the colon compared to other GI segments, and nilsodipine displays maximal absorption in the colon (reviewed in Rouge, et al. (1996)). Further, it is well accepted in the art that regional absorption of drugs in the GI tract is not well predicted by preclinical models (*see*, Hinderling, et al., *J. Clin. Pharmacol.*, 47(1):19-25 (2007) and Prior, *Business Briefing: Pharmatech*: 1-4 (2003), attached). Given the wide range of absorption spectra for drugs in different segments of the GI and the inability to predict these absorption spectra from preclinical models, it was not obvious that pulsed release formulations of milnacipran would be able to provide an efficacious dose over approximately 24 hours. This is supported by the fact that at the time Midha was published, the extent of absorption of milnacipran in the lower GI tract was unknown.

Only through a careful understanding of the relationship of the therapeutic formulation and dosage to plasma levels and the onset of side effects could a modified dosage form be designed that both (a) reduces, diminishes, or prevents locally mediated and centrally mediated side effects while (b) still providing a high enough dose to be efficacious. The present application discloses the pharmacokinetic profiles necessary to achieve this delicate balance between maintaining efficacy and reducing the incidence and/or severity of unwanted side effects and discloses the formulations necessary to achieve these profiles. Specific pharmacokinetic parameters are defined in claims 6-8. Midha does not disclose or suggest formulations exhibiting the parameters defined in claims 6-8.

Therefore, one of ordinary skill in the art, at the time of the present invention, would not have an expectation of success that a pulsatile release formulation of milnacipran could be developed that would deliver an efficacious dose while also reducing the incidence and/or intensity of unwanted side effects relative to immediate release milnacipran formulations.

As discussed above, Ansseau describes the efficacy and tolerance of fluoxetine versus milnacipran (abstract). Ansseau discloses that fluoxetine showed superior results versus milnacipran (page 135, first paragraph). Ansseau does not disclose or suggest a pulsatile release formulation of milnacipran that exhibits a therapeutic effect over 24 hours or methods of making and using thereof.

Further, Ansseau does not disclose or suggest a pulsatile release milnacipran formulation which exhibits diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects nor methods of making and using thereof. Although Ansseau does mention side effects associated with milnacipran and fluoxetine, Ansseau discloses that more patients dropped out of the fluoxetine study due to adverse effects than dropped out of the milnacipran study (page 133, first column, last paragraph).

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to formulate milnacipran as a pulsatile release dosage form because Midha teaches that pulsatile release formulations are useful for drugs which have a short half-life and must otherwise be administered two or three times daily and Ansseau discloses that milnacipran has a relatively short half-life. The Examiner has not considered the entire disclosure of Midha. Midha

discloses pulsatile release formulations of drugs that exhibit the potential for tolerance and abuse, namely methylphenidate. Milnacipran does not possess either of these properties. Midha does not disclose or suggest a pulsatile release milnacipran formulation that exhibits a therapeutic effect over 24 hours.

Ansseau describes comparative studies of *immediate release* milnacipran and fluoxetine formulations. Ansseau does not disclose or suggest a formulation, nor methods of making and using thereof, which provides a therapeutic effect over 24 hours. Ansseau discloses that milnacipran was less effective than fluoxetine and that this was likely due to the fact that only a single dose was administered, which led to inadequate plasma levels. Further, while Ansseau does briefly discuss the side-effects associated with milnacipran and fluoxetine, Ansseau does not disclose or suggest formulations which exhibit reduced incidence or intensity of side effects. Therefore, Ansseau does not provide the elements missing from Midha.

One of ordinary skill in the art would not be motivated to combine the pulsatile release methylphenidate formulations of Midha with the immediate release milnacipran formulations of Ansseau to arrive at the claimed methods since neither reference discloses or suggests pulsatile release formulations of milnacipran, nor methods of making and using thereof, that provide a therapeutic effect over 24 hours with reduced the frequency or severity of side effects. Even if one were motivated to combine the references, one of ordinary skill in the art would be motivated to prepare pulsatile release formulations containing fluoxetine, which showed superior results according to Ansseau. Neither of these references provide information that would lead

one of ordinary skill in the art to have a reasonable expectation of success of producing a pulsatile release formulation with the claimed properties.

The Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 1-10, 15-17 and 19-23. Accordingly, claims 1-10, 15-17 and 19-23 are not obvious over Midha in view of Ansseau.

Declaration showing unexpected results

A Declaration under 37 C.F.R. § 1.132 by Dr. Martin Keller demonstrating unexpected results is attached to this amendment and response. This declaration establishes that it was not obvious to develop a once-a-day formulation that would deliver a therapeutic dose of milnacipran while reducing the incidence and severity of side effects relative to immediate release milnacipran.

In the declaration, Dr. Keller states that a once-a-day formulation that has two separate and distinct "pulses" or releases of milnacipran would offer the benefit of providing a pharmacokinetic profile that closely mimics that of twice-a-day formulations which have demonstrated effectiveness in treatment of fibromyalgia. Dr. Keller further establishes that there is a wide range of absorption spectra for drugs in different segments of the GI and that it is not possible to accurately predict these absorption spectra from preclinical models, and therefore it was not obvious that pulsed release formulations of milnacipran would be able to provide an efficacious dose over approximately 24 hours. Dr. Keller describes how absorption of milnacipran in the lower intestine was not known at the time of the invention and that one of

ordinary skill in the art would not have been motivated to design and manufacture a dosage form which relies on complete absorption of the second release of milnacipran several hours after ingestion. The data that accompanies the declaration demonstrates the surprising result that the second release of milnacipran is *fully absorbed* several hours after ingestion and is effective to deliver plasma levels of milnacipran high enough to even be considered to be in the effective range for treatment of fibromyalgia.

These unexpected results are strong indicia of non-obviousness.

2. Midha in view of Ansseau and Menza

(a) Determining the scope and contents of the prior art

Midha and Ansseau are discussed above. Menza describes administering modafinil to augment a partial or nonresponse to an antidepressant (abstract). Menza does not disclose or suggest a pulsatile release milnacipran formulation as required by the claims.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The claimed compositions are discussed above.

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, Midha and Ansseau, alone or in combination, do not disclose or suggest a milnacipran formulation that provides pulsatile release of milnacipran with the claimed properties.

Menza discloses administering modafinil to augment a partial or nonresponse to an antidepressant. In contrast, the present claims require a milnacipran formulation *per se* that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours. Although dependent claims define other active agents that can be included in the formulation, these additional agents are not required to produce the claimed characteristics of the milnacipran formulation. It is the claimed milnacipran formulation itself that produces these results without a requirement for any additional agents. Further, Menza does not disclose milnacipran formulations with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. Menza is only concerned with formulations that potentiate efficacy of antidepressants and is silent with respect to effects on reducing the incidence or diminishing the intensity of any side effects. Menza does not cure the deficiencies of Midha and Ansseau. The Examiner has failed to establish a *prima facie* case of obviousness. Therefore, claims 1-10 and 15-23 are not obvious over Midha in view of Ansseau and Menza.

Declaration showing unexpected results

As discussed above, a Declaration under 37 C.F.R. § 1.132 by Dr. Martin Keller demonstrating unexpected results is attached to this amendment and response. The unexpected results presented therein, and discussed above, are strong indicia of non-obviousness.

3. Midha in view of Ansseau and Paillard

(a) Determining the scope and contents of the prior art

Midha and Ansseau are discussed above. Paillard describes a prolonged release pharmaceutical composition, for oral administration, containing a single daily dose of 60 to 140 mg of milnacipran (abstract). Paillard does not disclose a pulsatile release formulation as required by the claims.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The claimed compositions are discussed above.

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims. As discussed above, Midha and Ansseau, alone or in combination, do not disclose or suggest a milnacipran formulation that provides pulsatile release of milnacipran with the claimed properties. As discussed above, Paillard describes a prolonged release pharmaceutical composition, and not a pulsatile release formulation. Therefore, Paillard does not disclose the elements missing from Midha and Ansseau. One of ordinary skill in the art would not be motivated to combine the pulsatile release methylphenidate formulation of Midha with the immediate release formulation of Ansseau and the extended release formulation of Paillard to arrive at the claimed methods.

Paillard does not cure the deficiencies of Midha and Ansseau. The Examiner has failed to establish a *prima facie* case of obviousness. Therefore, claims 1-13, 15-17 and 19-24 are not obvious over Midha in view of Ansseau and Paillard.

Declaration showing unexpected results

As discussed above, a Declaration under 37 C.F.R. § 1.132 by Dr. Martin Keller demonstrating unexpected results is attached to this amendment and response. The unexpected results presented therein, and discussed above, are strong indicia of non-obviousness.

4. Rao

(a) Determining the scope and contents of the prior art

Rao discloses methods of treating visceral pain syndromes in a mammal (abstract). The method includes administering to the mammal an effective amount of a selective norepinephrine (NE)-serotonin (5-HT) reuptake inhibitor (NSRI), such as milnacipran (abstract). Rao generally discloses that compressed tablets can be formulated to provide delayed release, extended release, or repeat action release (page 12, paragraph 0209). However, Rao does not disclose or suggest a pulsatile release milnacipran formulation as defined in the claims.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S.P.Q. 698 (Fed. Cir. 1983).

The claimed compositions are discussed above.

The references alone or in combination do not disclose each and every element of the claims

In order to establish a *prima facie* case of obviousness, the references, alone or in combination, must disclose each and every element of the claims.

A pulsatile release dosage form is one that mimics a multiple dosing profile without repeated dosing and allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g. as a solution or prompt drug-releasing, conventional solid dosage form) (page 9, lines 5-11). A pulsatile release profile is characterized by a first dose of drug that is released substantially immediately following administration, followed by a period of no release followed by release of a first, and optionally a second, delayed release dose (page 9, lines 13-16). Pulsatile release is not the same thing as prolonged release.

The Examiner alleges that the formulation described in Example 41 of Rao is a pulsatile release formulation. The Examiner is incorrect. Example 41 in Rao describes a formulation containing immediate release and sustained release (i.e., extended release) doses. The formulation "results in a long-lasting slow and relatively regular release of the active ingredient" (page 25, paragraph 0361). This is not a pulsatile release formulation. As discussed above, a pulsatile release formulation is characterized by a first dose of drug followed by a period of no release, followed by release of a delayed release dose, etc. Rao does not disclose a pulsatile release formulation with these properties.

Rao does not disclose each and every limitation of the claimed formulations. The Examiner has failed to establish a *prima facie* case of obviousness. Therefore, claims 1-3, 6-17, 20 and 23 are not obvious over Rao.

Declaration showing unexpected results

As discussed above, a Declaration under 37 C.F.R. § 1.132 by Dr. Martin Keller demonstrating unexpected results is attached to this amendment and response. The unexpected results presented therein, and discussed above, are strong indicia of non-obviousness.

Double Patenting Rejection

Claims 1-9 and 11-22 were provisionally rejected under 35 U.S.C. 101 as claiming the same invention as claims 1-4 and 10-26 of copending Application Serial No. 11/192,697. Applicants respectfully traverse this rejection to the extent it is applied to the claims as amended.

Claims 1-3, 6-19 and 20-22 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-18 and 20-22 of copending Application Serial No. 10/691,936 in view of U.S. Patent No. 6,340,476 by Midha, et al. ("Midha") further in view of Ansseau, et al., Phsychopharmacology (1994) ("Ansseau"). Applicants respectfully traverse this rejection.

Claim 14 was rejected on the grounds of nonstatutory obviousness type double patenting over claims 1-3 and 9 of U.S. Patent No. 7,038,085 by Rariy, et al. ("Rariy") in view of Midha and Ansseau. Applicants respectfully traverse this rejection.

Legal Standard

Before consideration can be given to the issue of double patenting, two or more patents or applications must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement as set forth in 35

U.S.C. 103(c)(2) and (3) pursuant to the CREATE Act (Pub. L. 108-453, 118 Stat. 3596 (2004)). Congress recognized that the amendment to 35 U.S.C. 103(c) would result in situations in which there would be double patenting rejections between applications not owned by the same party (see H.R. Rep. No. 108-425, at 5-6 (2003)). For purposes of a double patenting analysis, the application or patent and the subject matter disqualified under 35 U.S.C. 103(c) as amended by the CREATE Act will be treated as if commonly owned. See also MPEP § 804.03. Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis.

Analysis

Claims 23 and 24 of the present application have been canceled. Claims 1-26 of U.S.S.N. 11/192,697 have been canceled. Accordingly, the Examiner's rejection of claims 1-9 and 11-22 as claiming the same invention as claims 1-4 and 10-26 of copending Application Serial No. 11/192,697 is no longer applicable. However, in order to facilitating prosecution, applicants' are willing to file a terminal disclaimer once the claims of the present application are in condition for allowance.

The double patenting rejection of claims 1-3, 6-19 and 20-22 as being unpatentable over claims 1-3, 6-18 and 20-22 of copending U.S.S.N. 10/691,936 in view of Midha and Ansseau is legally improper

The claims of the present application are directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity relative to one or more immediate release milnacipran side effects. In contrast, the claims of the '936 application are directed to a delayed release or extended release formulation of milnacipran.

The Examiner admits that the claims of the '936 application are not directed to pulsatile release milnacipran formulations (*see* page 15, second paragraph of the office action). However, the Examiner then goes on to cite the disclosures of Midha and Ansseau in an attempt to provide the elements missing from the claims. This is an obviousness analysis, not a double patenting analysis and is legally improper. Midha and Ansseau are discussed with respect to obviousness above.

As discussed above, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. As the Examiner admitted, the present claims are directed to pulsatile release formulations and the claims of the '936 application are directed to delayed and extended release formulations.

A "pulsatile release dosage form", as defined on page 16 of the specification, refers to a form that (1) mimics a multiple dosing profile without repeated dosing and (2) allows at least a

two-fold reduction in dosing frequency as compared to that drug presented as a conventional dosage form. The passage on page 16 goes onto state that a pulsatile release profile is characterized by a time period of no release (lag time) followed by rapid drug release. On page 8, lines 24-25, the specification discloses that the compositions are characterized by an initial rapid release of a therapeutically effective dose of milnacipran followed by so-called "delayed release" pulses such that a second and optional third delayed dose of the active agent are released from the dosage form. If a third dose is incorporated into the form, it is released after a period of no release (lag time) following release of the second dose. These delayed release pulses can be released immediately or can be released over an extended period of time. This definition does not encompass delayed release and extended release formulations, neither of which have an initial rapid release of a therapeutically effective dose of milnacipran, followed by a period of no release (lag time), followed by "delayed release" pulses such that a second and optional third delayed dose of the active agent is released from the dosage form.

Accordingly, claims 1-3, 6-19, and 20-22, as amended, are patentable over claims 1-3, 6-18, and 20-24 of copending U.S.S.N. 10/691,936.

The double patenting rejection of claim 14 over claims 1-3 and 9 of U.S. Patent No. 7,038,085 in view of Midha further in view of Ansseau is legally improper

The claims of the present application are directed to a milnacipran formulation that provides pulsatile release of milnacipran to produce a therapeutic effect over approximately 24 hours when administered to a patient in need, with diminished incidence or reduced intensity

relative to one or more immediate release milnacipran side effects. In contrast, the claims of the '085 patent are directed to an isolated compound of formula A and B, respectively. The claims of the '085 patent do not define a pulsatile release formulation.

The Examiner admits that the claims of the '085 patent are not directed to pulsatile release milnacipran formulations (*see* page 17, second paragraph of the office action). However, the Examiner then goes on to cite the disclosures of Midha and Ansseau in an attempt to provide the elements missing from the claims. This is an obviousness analysis, not a double patenting analysis, and is legally improper. In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is — does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? None of the claims in the '085 patent cited by the Examiner are directed to a pulsatile release formulation. Accordingly, claim 14 is patentable over claims 1-3 and 9 the '085 patent in view of Midha and Ansseau.

Allowance of claims 1-4, 6-12, and 14-22, as amended, is respectfully solicited.

Respectfully submitted,

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